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Alcohol Consumption, Family History of Hematolymphoproliferative Cancer, and the Risk of Non-Hodgkin's Lymphoma in Men

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PURPOSE: To investigate the association between alcohol consumption and the risk of non-Hodgkin's lymphoma (NHL) and to examine whether the association is modified by a family history of hematolymphoproliferative cancer (HLPC).
METHODS: Data on white men from two population-based case-control studies of NHL conducted in Iowa/Minnesota and Kansas were pooled for this analysis. Information on alcohol consumption, family history of HLPC, and other factors was obtained by interviewing 792 cases and 2193 controls or, if deceased, their next-of-kin. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).
RESULTS: There was no clear association between NHL and the use of alcohol, beer, hard liquor, or wine. The relationship, however, may differ according to a family history of HLPC. Alcohol use was not associated with the risk of NHL in men without a family history of HLPC (ORs = 0.8 and 0.9 for men consuming alcohol $\leq$ median and $>$ median, respectively), the presence of a family history in the absence of alcohol use was associated with a slightly increased risk (OR = 1.4; 95% CI 0.8–2.5), whereas risks of NHL among men with a positive family history were 2.1 (CI 1.0–4.7) for men consuming alcohol $\leq$ median (13.7 g/day) and 2.8 (1.3–5.9) for men consuming alcohol greater than median.
CONCLUSIONS: The present data found no clear association between alcohol consumption and the risk of NHL among men without a family history of HLPC, whereas alcohol intake was associated an elevated risk in men with a positive family history. The finding of effect modification of the alcohol-NHL association by a family history of HLPC is novel and requires confirmation.
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KEY WORDS: Alcohol, Family History, Lymphoma, Non-Hodgkin's Lymphoma.

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a cancer of the immune system, and immunosuppression due to a primary immunodeficiency disease (1) or acquired immune alterations (2) are established risk factors. High alcohol intake, either episodically or on a regular basis, is thought to be immunosuppressive, impairing both humoral and cell-mediated immunity (3), and could play a role in the development of NHL (4). Several epidemiologic studies (5–11) have evaluated the role of alcohol consumption in the etiology of NHL, but the findings have been inconsistent. One study found a significant positive association with beer consumption in men (5), three reported no association (6–8), one showed a weak inverse association in men (9), and two found a significant inverse association in women (10, 11). Differences in genetic susceptibility that predispose to differential environmental sensitivity could contribute to these inconsistencies (12). However, the interaction of genetic factors and alcohol consumption has never been investigated in previous epidemiologic studies of NHL.

To address this issue, we evaluated whether the effect of alcohol consumption on the risk of NHL is modified by a family history of hematolymphoproliferative cancer (HLPC), a surrogate of genetic susceptibility. Family history information has been commonly used as a crude indicator of genetic susceptibility when genetic markers are not available (13). We analyzed pooled data from two population-based, case-control studies conducted in three Midwestern states; Iowa, Minnesota, and Kansas, including the population previously reported by Brown and coworkers (9).

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Selected Abbreviations and Acronyms

NHL = Non-Hodgkin's lymphoma
HLPC = Hematolymphoproliferative cancer
OR = odds ratio
CI = confidence interval
IgM = immunoglobulin M

MATERIAL AND METHODS

Study Population

Data from two population-based, case-control studies of NHL conducted in Iowa/Minnesota (14) and Kansas (15) during the 1980s were pooled for this analysis. In the Iowa/Minnesota study, all newly diagnosed cases of NHL among white men, aged 30 years or older, were identified from the State Health Registry of Iowa records and a special surveillance of Minnesota hospital and pathology laboratory records (n = 780). The diagnostic period for eligibility was between March 1981 and October 1983 in Iowa, and between October 1980 and September 1982 in Minnesota. In Minnesota, cases that resided in the cities of Minneapolis, St. Paul, Duluth, or Rochester at the time of diagnosis were excluded because the original study focused on agricultural exposures. In Kansas, all cases of NHL among white men, aged 21 years or older, diagnosed between 1979 and 1981, were identified through the University of Kansas Cancer Data Service, a statewide tumor registry. A sample of 200 men was randomly selected from the 297 NHL cases diagnosed during the eligible time period. Pathology tissues were obtained to confirm the diagnosis. The response rates in the cases ranged from 89 to 96%.

Controls without hematopoietic or lymphatic cancer were selected by frequency matching on age, state of residence, and vital status using a 2:1 matching ratio in Iowa and Minnesota, and approximately 4:1 in Kansas. Controls for living cases under 65 years of age were randomly selected by random digit dialing, and those for cases 65 years or older were a simple random sample from the Health Care Financing Administration files. Controls for deceased cases were selected from death records in each state and matched to the cases by age and year of death. The response rates in the controls ranged from 77 to 93%.

Data Collection

Interviews were conducted with subjects, or next-of-kin, by telephone in Kansas, and by in-person interviews in Iowa and Minnesota. Participants were asked to indicate the usual consumption of three alcoholic beverages (wine, beer, and hard liquor) over their lifetime. For each type of alcoholic beverage, a commonly used unit — glass, can, "highball"—was specified. Participants were asked how many times, in an average week, they had consumed that amount of each alcoholic beverage. Responses were recorded separately for wine, beer, and hard liquor. Participants were also asked to provide a family history of cancer among biological parents and siblings, including type of cancer(s). Information on demographics, agricultural use of pesticides, occupational history, and other known or suspected risk factors for NHL was also collected.

Data Analysis

There were 792 cases and 2193 controls in the combined study. The number of subjects by state of residence was 293 cases (228 living, 65 deceased) and 603 controls (423 living, 180 deceased) for Iowa; 329 cases (201 living, 128 deceased) and 642 controls (403 living, 239 deceased) for Minnesota; and 170 cases (79 living, 91 deceased) and 948 controls (452 living, 496 deceased) for Kansas.

The weekly alcohol intake, in grams, was calculated by multiplying the amount of each alcoholic beverage consumed by the ethanol content of the specific beverage. Average weekly intake was calculated by summing the contribution from each type of alcoholic beverage.

Individuals were classified *a priori* according to four levels of alcoholic beverage consumption: non-drinkers were defined as individuals who reported that their total alcohol use was zero; and the three other categories were based on tertile cut-points among controls for each type of alcoholic beverage.

A family history of HLPC and other variables of interest were categorized into natural categories. Since the reliability of data on second-degree relatives is low (16), our analyses of the effect of a family history of HLPC used only data on the parents, brothers, sisters, and children (first-degree relatives). The presence of HLPC in at least one first-degree relative was considered a positive family history. HLPC rather than NHL was used in the definition of a positive family history because: 1) hematopoietic stem cells are the common cellular origin for a variety of hematological cancers including NHL; 2) both hematological cancers and NHL may share common risk factors; and 3) respondents might not be able to distinguish between the various types of hematological cancers when they reported a family history of NHL or other hematological cancers.

The maximum likelihood estimate of the odds ratio (OR) (17) and the 95% confidence interval (CI) were used as the measure of association between exposure categories and the risk of NHL. Multiple logistic regression analysis was used to adjust the relative risk of NHL from alcohol consumption for the possible effect of confounding factors. These variables included age ($\leq$ 55, 56–65, 66–75, $>$ 75 years), marital status (current, former, or never), state of residence (Iowa, Minnesota, Kansas), type of respondent (living, proxy), first-degree relatives with HLPC (yes, no),

use of herbicides (yes, no), and use of tobacco products (yes, no). Information on HIV infection was not available. However, it seems unlikely that HIV infection was a significant confounder or risk factor for NHL in the present study, given the time period (i.e., in the early to mid-80s), location (i.e., three Midwestern states where HIV infection and AIDS were not common), and age of the participants (i.e., 84% of the cases and 79% of the controls were older than 50 years of age).

To evaluate the possible effect modification of the alcohol-NHL association by a family history of HLPC, cases and controls were classified by both family history of HLPC and alcohol consumption, and ORs were calculated for a positive family history, with or without alcohol consumption, and for a negative family history with alcohol consumption, each being compared with the absence of both family history and alcohol consumption. To maximize the number of subjects in the multivariable analysis, an additional level was created to contain those with missing data for family history or specific type of alcoholic beverages under analysis and those who used alcoholic beverages other than the specific type of alcoholic beverages under analysis. When testing for trend, the exposure measure was entered as an ordinal variable into the model. A test for non-linear trend was also conducted and found not to be significant. Inclusion or exclusion of proxy data did not materially change the point estimates or observed associations. Thus, proxy data were included in the present report. Analyses were conducted using SAS (SAS Institute, Cary, NC) software programs. The reported *p*-values are two-sided.

TABLE 1. Age-adjusted odds ratios (OR) of non-Hodgkin lymphoma according to characteristics of the white men in this case and control study

Characteristics	No. of controls[a]	No. of cases[b]	OR[c]	95% CI[d]
Education				
<High school	960 (44%)	361 (46%)	1.0	Referent
High school	514 (24%)	189 (24%)	1.0	0.8–1.2
>High school	698 (32%)	239 (30%)	0.9	0.8–1.1
Marital status				
Current	1711 (78%)	657 (83%)	1.0	Referent
Former	322 (15%)	97 (12%)	0.8	0.6–1.0
Never	160 (7%)	38 (5%)	0.6	0.4–0.9
Tobacco				
Never	504 (23%)	166 (21%)	1.0	Referent
Ever	1686 (77%)	625 (79%)	1.1	0.9–1.4
Worked/Lived on a farm				
Never	596 (27%)	189 (24%)	1.0	Referent
Ever	1590 (73%)	597 (76%)	1.2	1.0–1.4
Used herbicides				
Never	682 (56%)	223 (50%)	1.0	Referent
Ever	536 (44%)	222 (50%)	1.3	1.0–1.6
Used 2,4-D				
Never	770 (70%)	273 (64%)	1.0	Referent
Ever	335 (30%)	151 (36%)	1.3	1.0–1.6
First degree relatives with HLPC				
No	2104 (97%)	728 (93%)	1.0	Referent
Yes	55 (3%)	51 (7%)	2.6	1.8–3.9
First degree relatives with cancers				
No	1194 (55%)	334 (43%)	1.0	Referent
Yes	965 (45%)	445 (57%)	1.6	1.4–1.9

[a]Number of controls may not sum to 2193 due to missing data.
[b]Number of cases may not sum to 792 due to missing data.
[c]OR = age-adjusted odds ratios by 10-years groups using the method of Mantel and Haenszel.
[d]CI = confidence interval.

RESULTS

The characteristics of the study subjects and the possible risk factors for NHL are shown in Table 1. The median age of both the cases and controls was 57 years (data not shown). In comparison with the controls, cases were more likely to be currently married, more likely to have ever lived or worked on a farm, have ever used herbicides or 2,4-D, and more likely to have first degree relatives with cancer or HLPC. Cases and controls were similar with respect to education and tobacco use.

Table 2 shows the age- and multivariable-adjusted ORs for NHL according to levels of intake of different alcoholic beverages, with the non-drinkers of all alcohol beverages representing the reference category for each specific type of alcoholic beverage. The ORs for NHL were not associated with alcohol intake of any type. There were slight decreases in the risk of NHL with alcohol consumption. Men in the three tertiles of alcohol intake had a consistently lower risk of developing NHL compared with men who had not used any alcohol, but these decreases were not statistically significant and there was no monotonic trend. The ORs for drinkers of beer, liquor, or wine were also less than 1.0, and again there were no consistent exposure-response gradients. We also analyzed data for proxies and direct interviews separately, and found that the point estimates were similar (data not shown). Subgroup analyses according to the Working Formulation (18) (i.e., diffuse, follicular, small lymphocytic, and all other NHL) showed similar patterns to those seen for total alcohol use (data not shown). However, the sample size of cases of specific NHL subtype with a family history was not large enough for precise evaluation of effect modification by family history.

A family history of HLPC increased the risk of NHL (OR = 2.6; 95% CI = 1.8–3.9). To evaluate the possible effect modification of the alcohol-NHL association by a family history of HLPC, cases and controls were classified by both family history of HLPC and alcohol consumption (Table 3). There was no risk of NHL from alcohol use among men without a family history of HLPC (ORs = 0.8 and 0.9 for men consuming alcohol $\leq$ median and $>$ median, respectively), but the risk was elevated among men

TABLE 2. Age and multivariable-adjusted odds ratios[a] of non-Hodgkin's lymphoma among white men in relation to the level of intake of various alcoholic beverages

		Tertile of intake			
Alcohol	Non-drinkers	I (low)	II	III (high)	*p*-trend
Alcohol, g per week					
Range	None	≤71.7	71.8–205.7	>205.7	
No. of cases/controls	364/889	121/427	152/423	152/427	
OR[a] (age-adjusted)	1.0	0.7	0.9	0.9	0.21
OR[b] (full model)	1.0	0.8	0.9	0.8	0.25
95% CI	(Referent)	(0.6–1.0)	(0.7–1.1)	(0.7–1.1)	
Beer, servings per week					
Range	None	≤2	3–10	>10	
No. of cases/controls	364/889	80/288	137/383	119/320	
OR[a] (age-adjusted)	1.0	0.7	0.9	0.9	0.26
OR[b] (full model)	1.0	0.8	0.9	0.9	0.26
95% CI	(Referent)	(0.6–1.1)	(0.7–1.1)	(0.7–1.1)	
Liquor, servings per week					
Range	None	≤2	3–9	>9	
No. of cases/controls	364/889	77/273	98/265	94/276	
OR[a] (age-adjusted)	1.0	0.7	0.9	0.8	0.11
OR[b] (full model)	1.0	0.8	0.9	0.8	0.22
95% CI	(Referent)	(0.6–1.1)	(0.7–1.2)	(0.6–1.1)	
Wine, servings per week					
Range	None	≤1	2–3	>3	
No. of cases/controls	364/889	29/135	20/67	40/95	
OR[a] (age-adjusted)	1.0	0.5	0.7	1.0	0.30
OR[b] (full model)	1.0	0.7	0.8	1.0	0.43
95% CI	(Referent)	(0.4–1.0)	(0.5–1.3)	(0.6–1.5)	

[a]Odds ratios (OR) and 95% confidence intervals (CI), adjusted for age (≤55, 56–65, 66–75, >75 years).
[b]OR (full model) adjusted for age (≤55, 56–65, 66–75, >75 years), marital status (current, former, or never), state of residence (Iowa, Kansas, Minnesota), type of respondent (living, proxy), first degree relatives with hematolymphoproliferative cancer (yes, no, missing), use of herbicides (yes, no, missing), and use of tobacco products (yes, no).

with a positive family history of HLPC. Using non-drinkers with a negative family history of HLPC as the referent, we found the risks of NHL among men with a positive family history of HLPC were 1.4 (CI = 0.8–2.5) for non-drinkers, 2.1 (CI = 1.0–4.7) for men consuming alcohol ≤ 13.7 g/day, and 2.8 (CI = 1.3–5.9) for men consuming alcohol greater than 13.7 g/day. The use of beer, hard liquor, and wine also showed the similar patterns.

Use of tobacco products, or having lived or worked on a farm or ranch did not significantly modify the risk of NHL associated with alcohol consumption (data not shown).

DISCUSSION

In this pooled analysis of data from two population-based, case-control studies, there was no clear association between NHL and the use of alcohol, beer, hard liquor, or wine. The ORs for alcohol consumption were generally less than 1.0. This relationship, however, appeared to be modified by a family history of HLPC. Alcohol use was not associated with the risk of NHL in men without a family history of HLPC. However, the presence of a family history of HLPC in the absence of alcohol use was associated with a slightly increased risk (OR = 1.4), whereas the presence of both factors was associated with ORs of 2.1 and 2.8 for the two levels of alcohol intake. The OR patterns of the separate effects of beer, hard liquor, and wine were similar to total alcohol intake.

Our finding of little association of NHL with alcohol consumption in men is consistent with some, but not all, published studies (5–11). Brown and colleagues (9), also using data from the Iowa/Minnesota study, found that the ORs for drinkers of any type of alcohol were slightly less than 1.0 for NHL and its subtypes, except for diffuse lymphoma. Nelson and coworkers (10), in a population-based study, found that the risk of NHL among women decreased significantly with increased consumption of alcoholic beverages, with a risk 50% lower among those consuming five or more drinks per week compared to non-drinkers. In that study, a statistically significant inverse association was not observed in men, although the point estimates for each type of alcoholic beverage were similar to those for women.

In a prospective cohort study of Iowa women, Chiu and coworkers (11) reported a statistically significant inverse association between alcohol consumption and NHL, with a 22% and 40% decreased risk for women with intakes of alcohol ≤ 3.4 g per day and > 3.4 g per day, respectively,

TABLE 3. Multivariable ORs[a] of non-Hodgkin's lymphoma by level of intake of various alcoholic beverages and family history of hematolymphoproliferative cancer (HLPC) among first-degree relatives

			Level of intake					
			Non-drinkers		⩽Median		> Median	
			Cases	Controls	Cases	Controls	Cases	Controls
Family history		Alcohol						
	No	Number	338	846	172	617	215	618
		OR (CI)	1.0 (referent)		0.8 (0.6–0.9)		0.9 (0.7–1.1)	
	Yes	Number	20	29	13	13	18	12
		OR (CI)	1.4 (0.8–2.5)		2.1 (1.0–4.7)		2.8 (1.3–5.9)	
Family history		Beer						
	No	Number	338	846	67	269	195	520
		OR (CI)	1.0 (referent)		0.7 (0.5–0.9)		0.9 (0.7–1.1)	
	Yes	Number	20	29	9	8	15	8
		OR (CI)	1.3 (0.7–2.4)		2.5 (0.9–6.7)		3.5 (1.5–8.5)	
Family history		Hard Liquor						
	No	Number	338	846	104	414	137	372
		OR (CI)	1.0 (referent)		0.7 (0.5–0.9)		0.9 (0.7–1.2)	
	Yes	Number	20	29	14	9	7	8
		OR (CI)	1.4 (0.7–2.5)		3.1 (1.3–7.4)		1.6 (0.6–4.5)	
Family history		Wine						
	No	Number	338	846	29	132	50	154
		OR (CI)	1.0 (referent)		0.7 (0.5–1.1)		0.8 (0.6–1.2)	
	Yes	Number	20	29	4	6	5	2
		OR (CI)	1.4 (0.8–2.6)		1.4 (0.4–5.2)		4.8 (0.9–25.4)	

[a]OR (full model) adjusted for age (⩽55, 56–65, 66–75, >75 years), marital status (current, former, or never), state of residence (Iowa, Kansas, Minnesota), type of respondent (living, proxy), use of herbicides (yes, no, missing), and use of tobacco products (yes, no).

when compared to women who did not drink alcohol. Since we saw no evidence for a dose-response relationship in the present study, our findings of slight deficits with alcohol consumption are probably inconsequential. It is difficult to postulate a gender-specific causal association for alcohol consumption. It remains possible, however, that men and women have different distributions on alcohol use and may have different risk factors for NHL. Unfortunately, our data were not able to address this issue. Additional studies on alcohol use and NHL among women are needed.

Of potential interest was our finding that the use of alcoholic beverages, including beer, hard liquor, and wine among men with a family history of HLPC increased the risk of NHL from 1.4 to about 2.5. Although a family history of NHL or other HLPC in a first-degree relative has been suggested as a risk factor for NHL (6, 19–21), as was also observed in these data, the extent to which both familial predisposition enhancing an individual's susceptibility to lymphoma and the effects of common environmental exposures contribute to lymphomagenesis has not been fully explored (22). To our knowledge, no previous epidemiologic study has examined the association between alcohol consumption and NHL risk in individuals with and without a family history of HLPC. It remains possible that our finding could be due to chance because the difference between ORs by alcohol consumption among those with a family history of HLPC was small.

Results from a recent case-control study of 1511 NHL cases showed that the association of NHL with familial HLPC is stronger in patients diagnosed at age 45 years and older than in young patients (20). This increased risk among older patients suggests a role for cumulative environmental exposures or a certain mode of genetic control, or both. Studies in animals have shown that multiple factors are involved in oncogenesis. These include external factors such as exposure to radiation, chemicals and viruses, in addition to the hosts' immunologic and genetic makeup, and that these various factors can combine in different ways to result in neoplastic change (23). It is possible that inherited genetic variations involving multiple genes may influence the exposure of lymphoid cells to environmental agents and, thus, influence the likelihood of any individual developing NHL (23).

Individuals from families with recurrence of HLPC may have an increased genetic susceptibility (due to metabolic polymorphisms, oncogene expression, tumor suppress gene deletion, or other mechanisms) to the effects of environmental or other potential cancer-causing agents (22). For example, it has been found that siblings of HLPC cases, who are not affected by the tumors, have abnormalities of both humoral and cellular immunity, including increased immunoglobulin M (IgM) (24); decreased IgG, IgM, or IgA; and decreased skin-test hypersensitivity and lymphocyte responsiveness (25). It is plausible that such individuals may have an increased susceptibility to the effects of

alcohol, or to other substances whose mutagenic or carcinogenic effects may be enhanced by alcohol consumption (26–29). There is indirect evidence that, in most hematological malignancies, the first stage of malignant transformation often occurs in a pluripotent hemopoietic stem cell (30, 31). It has been hypothesized that a second hit, possibly due to environmental factors, may then lead to the occurrence of hematological malignancy (32). Therefore, it is possible that, in these individuals, alcohol consumption may give rise to the secondary changes necessary for the development of NHL, although this is admittedly speculative.

Second, our findings that the use of beer, hard liquor, and wine showed similar patterns to those seen for total alcohol use suggest that ethanol *per se* is responsible. Ethanol is oxidized to acetaldehyde, which has been recognized as a carcinogen in experimental animals (29). Acetaldehyde can induce sister chromatid exchanges in human cells (33), and an elevation of chromosomal aberrations in lymphocytes of alcoholics has been reported (34). The production of acetaldehyde is under polymorphic genetic control (e.g., alcohol dehydrogenase 3) (29) and, therefore, might show familial aggregation. Finally, although family history may be a crude indicator of greater genetic susceptibility to the effect of alcohol use, it is possible that it may also reflect shared environmental exposures among the family members. This may be particularly true in the present study since a positive family history is defined as at least one first-degree relative with a hematolymphoproliferative cancer.

We found that alcohol consumption was a risk factor for NHL only among individuals with the appropriate inherited genetic susceptibility (e.g., somatic mutation, or abnormalities of humoral or cellular immunity), but had no effect on the risk of NHL among individuals without such inherited genetic factors. There is no evidence to date that alcohol itself is a carcinogen for NHL (26). To the contrary, mechanisms have been suggested by which moderate or social use of alcohol might be protective against NHL, including its effect on insulin levels or antioxidant micronutrients in the alcoholic beverages (11).

Consideration must also be given to potential limitations in the present study that may have led to the observed associations. The specifics on a family history of HLPC were obtained from interviews with subjects or their next-of-kin without medical record validation, and could have been biased. However, self-reporting of cancer in first-degree relatives has been shown to be relatively accurate (35). In a case-control study of 437 NHL cases in Yorkshire, England, the OR was only slightly reduced when the analysis was restricted to confirmed (by medical record) occurrences of leukemia or lymphoma among relatives (6). Case-response bias is another concern in our study. However, an evaluation of possible recall bias among chronic lymphocytic leukemia cases, cancer controls, and non-cancer controls in a case-control study showed little evidence of differential recall regarding family history among cancer versus non-cancer subjects (19). Inaccurate information from proxy respondents is another concern. We calculated the ORs using direct and proxy interviews data separately, and found that the directions of association were consistent regardless of inclusion or exclusion of proxy respondents. Another potential limitation is that the diagnosis of NHL may result in cases differentially report their alcohol consumption compared with controls, which may bias our risk estimates. Finally, it remains possible that the risk estimates for the alcohol consumption in men with a family history lack precision due to small numbers.

Our study also has several strengths, including the large number of subjects in the combined dataset, which provided greater power to evaluate the potential for effect modification of the association between alcohol consumption and NHL risk by a family history of HLPC. The pooled dataset also permitted more valid and precise conclusions regarding the exposure-disease relationship than is possible with a meta-analysis (36). Other strengths of this study include: 1) high response rates (89–96% for cases and 77–93% for controls); 2) inclusion of newly-diagnosed, histologically-confirmed cases of NHL that occurred in defined time periods; 3) a randomly selected population group control representative of the population at large; and 4) availability of information on most possible confounding factors.

In summary, the present study found no clear association between alcohol consumption and the risk of NHL among men without a family history of HLPC, whereas alcohol intake was associated with an elevated risk in men with a positive family history. The finding of effect modification of the alcohol-NHL association by a family history of HLPC is novel and needs confirmation. Future studies should critically evaluate the role of alcohol consumption and genetic factors in both the study subjects and their family members to better understand this relationship.

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